Treatment sequence with either irinotecan/cetuximab followed by FOLFOX-4 or the reverse strategy in metastatic colorectal cancer patients progressing after first-line FOLFIRI/bevacizumab: An Italian Group for the Study of Gastrointestinal Cancer phase III,

This is the author's manuscript

Original Citation:

Treatment sequence with either irinotecan/cetuximab followed by FOLFOX-4 or the reverse strategy in metastatic colorectal cancer patients progressing after first-line FOLFIRI/bevacizumab: An Italian Group for the Study of Gastrointestinal Cancer phase III, randomised trial comparing two sequences of therapy in colorectal metastatic patients / Cascinu, Stefano; Rosati, Gerardo; Bilancia, Domenico; Nasti, Guglielmo; Iaffaioli, Rosario Vincenzo; Lonardi, Sara; Zagonel, Vittorina; Zaniboni, Alberto; Marchetti, Paolo; Romiti, Adriana; Leone, Francesco; Aglietta, Massimo; Giordano, Monica; Corsi, Domenico C.; Ferrà, Francesco; Labianca, Roberto; Mosconi, Stefania; Ronzoni, Monica; Gianni, Luca; Rulli, Eliana; Poli, Davide; Galli, Francesca; Torri, Valter; De Simone, Irene; Galli, Fabio; Pasini, Felice; Rangoni, Giovanni; Vannetti, Enrico; Genitori, Rossana; Rosina, Antonino; Ferrarini, Rossana; Mosca, Fabio; Cozzi, Lorena; Cascinu, Stefano; Rosati, Gerardo; Bilancia, Domenico; Nasti, Guglielmo; Iaffaioli, Rosario Vincenzo; Lonardi, Sara; Zagonel, Vittorina; Zaniboni, Alberto; Marchetti, Paolo; Leone, Francesco; Giordano, Monica; Corsi, Domenico C.; Ferrà, Francesco; Labianca, Roberto; Ronzoni, Monica; Scartozzi, Mario; Galli, Francesca. - In: EUROPEAN JOURNAL OF CANCER. - ISSN 0959-8049. - Sep;83(2017), pp. 106-115.

Published version:

DOI:10.1016/j.ejca.2017.06.029

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Original Research

Treatment sequence with either irinotecan/cetuximab followed by FOLFOX-4 or the reverse strategy in metastatic colorectal cancer patients progressing after first-line FOLFIRI/bevacizumab: An Italian Group for the Study of Gastrointestinal Cancer phase III, randomised trial comparing two sequences of therapy in colorectal metastatic patients

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Received 14 February 2017; received in revised form 16 June 2017; accepted 29 June 2017
Available online 20 July 2017

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KEYWORDS
Metastatic colorectal cancer;
Treatment strategy;
K-RAS wild type;
Cetuximab;
Treatment sequence

Abstract
Introduction: The optimal treatment strategy for RAS wild type (WT) mCRC is controversial. Our phase III study investigated the effect of introducing earlier (second-line) or later (third-line) cetuximab in patients progressed after FOLFIRI/bevacizumab first-line.

Patients and methods: mCRC patients progressing after FOLFIRI/bevacizumab first-line were randomised to receive second-line irinotecan/cetuximab followed by third-line FOLFOX-4 (arm A) or the reverse sequence (arm B). Primary end-point was progression-free survival (PFS).

Results: About 54 and 56 patients were randomised in arm A and in arm B, respectively. After a median follow-up of 37.5 months, 100 PFS events were recorded. Median PFS was 9.9 months in arm A and 11.3 months in arm B (Hazard ratio [HR] 1.04, 95% confidence interval [CI]: 0.69—1.56, \( p = 0.854 \)), while median overall survival was 12.3 months in arm A and 18.6 months in arm B (HR 0.84, 95% CI: 0.55—1.28; \( p = 0.411 \)). No overall difference in side-effects were observed between the two treatment arms.

Conclusions: This trial did not meet the primary end-point (PFS). Like other preclinical and clinical evidences, our study seems to suggest a reduced activity of cetuximab after a first-line bevacizumab-based therapy.

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1. Introduction

Colon cancer is the second most common malignant disease in developed countries [1]. The introduction of treatment options such as oxaliplatin and irinotecan combinations, and more recently agents directed against the epidermal growth factor receptor (EGFR, cetuximab and panitumumab) or tumour-driven angiogenesis (bevacizumab, afiblercept and ramucirumab) determined an impressive improvement in median overall survival (OS) from the initial 6 months to the current 30 months. Concomitantly, the extensive use of effective predictive markers also represented a new successful opportunity in order to select the best treatment for each patient. The translation into clinical practice of the use of K-RAS first and K-RAS and N-RAS then for EGFR-targeted agents opened, in fact, the way to a true personalised approach [2].

In spite of these encouraging results, several controversial issues remain unanswered. In particular, the definition of the best up-front combination as well as the optimal treatment sequence is still a matter of debate, especially in RAS wild-type tumours.

The present trial, initially designed in 2008, aimed to verify different clinical assumptions about the optimal first-line treatment and the global therapeutic strategy for metastatic colorectal cancer patients. Although we knew that either first-line FOLFOX or FOLFIRI were equally active, findings from the GERCOR study suggested that FOLFOX second-line might determine a better response rate (RR) and progression-free survival (PFS) in this setting [3]. Furthermore, at the time when the present study was designed first-line bevacizumab-based therapy preferentially included irinotecan. Based on these considerations we then decided to investigate the use of FOLFOX second-line in metastatic colorectal cancer patients progressing after first-line irinotecan-based chemotherapy.

Further considerations in the specific subset of RAS wild type (WT) colorectal tumours might suggest that cetuximab in combination with chemotherapy represented a preferable choice over bevacizumab [4]. Nevertheless cross comparisons of clinical data also indicated that on the one hand the clinical activity of bevacizumab faded across subsequent treatment lines, while on the other hand cetuximab retained a comparable clinical activity throughout all lines [5—7]. These findings implied that cetuximab was in fact the only effective treatment available for third-line therapy within a possible treatment strategy, particularly, when neither regorafenib nor TAS-102 was available [8,9].

Taking all these assumptions into account we designed a phase III randomised trial to compare the efficacy and safety of two different treatment sequences: second-line irinotecan/cetuximab followed by third-line FOLFOX-4 versus second-line FOLFOX-4 followed by third-line irinotecan/cetuximab in K-RAS WT patients progressing after first-line FOLFIRI/bevacizumab.

Although both these treatment strategies were considered a standard of care approach in 2008, findings from the FIRE-3, CALGB and PEAK trials [10—12] recently indicated that EGFR inhibitors in combination with chemotherapy might now be the preferred first-line choice in RAS WT tumours. Moreover, second-line treatment with EGFR-directed monoclonal antibodies may be currently questioned in view of the bevacizumab beyond progression strategy as suggested by the TML and BEBYP trials [13,14].
2. Patients and methods

The COMETS trial was an open-label, multicentre, phase III, randomised study conducted in 12 clinical Centres across Italy. The trial was approved by the Institutional Review Boards at all participating Sites and was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all participating patients before random assignment.

Two substantial amendments to study design were performed. The first one, on November 2008, not allowing the inclusion of mutated KRAS patients based on the absence of clinical benefit from anti-EGFR treatment in KRAS-mutant patients. These findings along with more robust first-line data for anti-EGFR monoclonal antibodies encouraged the use of first-line cetuximab (instead of bevacizumab as planned and specified in the study protocol) in combination with chemotherapy in K-RAS WT patients and eventually, resulted in a lower accrual rate. On June 2012, the Steering Committee of the trial concluded that the scientific question posed by the study was still of interest, and therefore, in order to improve study feasibility the primary end-point was changed from OS to PFS. This modification led to a reduction of the sample size from 350 patients to 110 patients. Globally we believed that PFS could be a good surrogate for OS. In fact we estimated that a PFS increase of at least 3 months after the third-line could indicate an increase in OS as well.

2.1. Patients and study procedures

Patients aged ≥18 years and ≤75 years with histologically confirmed K-RAS exon 2 WT metastatic colorectal cancer progressing after a first-line treatment with FOLFIRI/bevacizumab and with an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1 were enrolled. Patients were required to have an adequate haematological, hepatic and renal function, no other malignancies within 5 years before enrolment, no history or presence of other clinically significant diseases, metabolic dysfunction, physical examination or laboratory findings or any other medical conditions that might contraindicate the use of the investigational drugs.

2.2. Treatment plan

Patients were randomly assigned in a 1:1 ratio to one of the two treatment sequences under investigation: second-line irinotecan/cetuximab followed by third-line FOLFOX-4 (arm A) versus second-line FOLFOX-4 followed by third-line irinotecan/cetuximab (arm B). The randomisation process was performed using a block design randomisation procedure stratified according to recruiting center via a central randomisation service. All randomised patients received a unique number allowing identification throughout the trial on all study documentation related to that subject before any study-specific procedures.

K-RAS exon 2, codons 12–13 mutational status was assessed before randomisation in formalin-fixed, paraffin-embedded tumour tissue sections according to the national guidelines for the identification of K-RAS status. Cetuximab was administered intravenously (i.v.) at an initial dose of 400 mg/m² followed by 250 mg/m², on day 1 of each 7-day cycle. Irinotecan was administered as a 30–90 i.v. infusion at a dose of 180 mg/m² on day 1 of a 2-week cycle.

The FOLFOX-4 regimen consisted of a 2-hour i.v. infusion of oxaliplatin 85 mg/m² on day 1, a 2-hour i.v. infusion of leucovorin 100 mg/m² on day 1 and 2, a bolus i.v. infusion of 5-fluorouracil 400 mg/m² on day 1 and 2 and a 22-hour i.v. continuous infusion of 5-fluorouracil 600 mg/m² on day 1 and 2 of a 2-week cycle.

Treatments were considered as completed when continued until disease progression.

2.3. Assessments

Medical history, complete physical examination (including weight and ECOG PS assessment) and routine blood and urine tests were performed within 7 d of starting treatment, on day 1 of every cycle, within 30 d after the end of treatment and then every month until disease progression.

A computed tomography (CT) scan of the chest and the abdomen and/or a magnetic resonance imaging (MRI) of the abdomen were performed within 4 weeks of starting study treatment and repeated after every 12 weeks until disease progression and within 30 d after the end of treatment. Study protocol required that the same radiological imaging technique (CT or MRI) performed at the time of patient’s screening was to be used for all subsequent tumour evaluations. Tumour response was evaluated by investigators’ assessment and according to the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) [15]. After disease progression, patients were followed every month to collect the data on OS and post-study cancer treatment.

Any adverse events (AEs) occurring from the day of the first dose of each treatment through 30 d after the day of the last dose were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0). Skin-related or nail-related toxicities were graded using NCI-CTCAE, version 3.0 with modifications.

2.4. Statistical analysis

The primary end-point of the study was PFS, defined as the time from the date of randomisation up to the date
of progression after third-line treatment or death from any cause, whichever comes first. Patients who never started the third-line treatment, without tumour progression during second-line treatment or deceased while on study were censored at the last tumour assessment date.

Secondary end-points included the PFS in second-line treatment (PFS II), defined as the time from the date of randomisation up to the date of first progression after second-line or death from any cause; the OS, defined as the time from the date of randomisation to the date of death from any cause and the RR (RR), defined as the proportion of patients showing a complete or partial best tumour response according to the RECIST criteria. RR was analysed for second and third-line treatment, separately.

The proportion of the maximum grade reached for each AE separately analysed during 2nd and 3rd-line was established as a secondary safety end-point.

Three explorative analyses were performed. The first one on the PFS in thirdline treatment (PFS III), defined as the time from the third-line starting date up to the date of first progression after third-line or death from any cause. Furthermore, the overall RR, defined as the proportion of patients reached a complete or partial best tumour response during the second or third-line treatment, was calculated and analysed. PFS and OS were finally analysed separately according to primary tumour location. Splenic flexure, descending and sigmoid colon and recto-sigmoid junction were defined as left colon, whereas right colon included the ascendant colon, the hepatic flexure and the traverse colon.

To achieve a power of 80% of detecting a hazard ratio (HR) of 0.57 in favour of one of the two sequences, translating into an increase of median PFS from 4 to 7 months, with a two-sided type I error of 5%, using the Mantel-Cox version of the log-rank test, 110 patients needed (101 PFS events).

PFS and OS analyses were based on the modified intention-to-treat (mITT) population, which encompassed all randomly assigned patients with no major violation of eligibility criteria, irrespective of whether the patient received any study drugs. Kaplan–Meier curves were estimated and survival was summarised with the median and the interquartile range (IQR). The impact of potential confounders was explored in a Cox proportional hazard model including clinical/biological features as covariates (sex, age, ECOG PS and metastases site). HRs and 95% confidence intervals (95% confidence intervals [CIs]) were estimated. Overall RR and RR during second-line (RR II) were analysed on the RR analysis set II, which included all the mITT patients who received at least one dose of second-line treatment and with at least one target lesion evaluated during second-line. RR during three-line (RR III) was analysed on the RR analysis set III, which included all patients who received at least one dose of third-line treatment and with at least one target lesion evaluated during third-line. Rates were compared between arms by chi-square test.

Safety end-points were analysed on the safety analysis set II, which included all the mITT patients who received at least one dose of second-line treatment, and on safety analysis set III, which included all the mITT patients who received at least one dose of third-line treatment.

The distributions of maximum grade reached for each AE per subject were compared between the arms by chi-square test for trend.

All serious AEs (SAEs) were described for each treatment arm with the number and proportion of patients presenting any SAE, severity, suspected relationship to study medication and outcome. Statistical analyses were performed using the SAS® System program package for Windows (version 9.4). This trial is registered with ClinicalTrials.gov, number NCT01030042.

2.5. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit

3. Results

Between 30th September 2009 and 8th April 2015, 110 patients were randomised to one of the two chemotherapy sequences. The trial profile is summarised in Fig. 1. Two patients with major violation of eligibility criteria were excluded from the mITT analysis set (one patient had a KRAS mutation and no data were available for the other one). One patient and 39 patients were excluded, respectively, from Safety Analysis Set II and from Safety Analysis Set III since they did not undergo second or third-line treatment. One hundred and four patients who received at least one dose of second-line treatment and with at least one target lesion evaluated during second-line, and RR during three-line were included in the RR Analysis Set II and in the RR Analysis Set III, respectively. Baseline characteristics are reported in Table 1.

Thirty-six patients (69%) in arm A and 40 patients (73%) in arm B completed the second-line treatment until disease progression. Only 14% and 12% of these patients in arm A and B, respectively, completed the assigned treatment without schedule change and/or dose modification. The main reason of treatment interruption was medical decision in both arms. Thirty-one patients in arm A and thirty-nine patients in arm B started the third-line treatment. Twenty-three patients and twenty-nine patients continued treatment until disease progression. Only 9% and 17% of these patients in arm A and B, respectively, completed the assigned treatment
without schedule change and/or dose modification. The main reason for failure to start treatment or treatment interruption was medical decision in both arms. At the time of database lock (4th April 2016), only one patient in arm A was still on treatment.

The hazard proportionality assumption was assessed and satisfied for all the survival end-point. At a median follow-up of 37.5 months (IQR 30.2–59.6) 100 patients had progression or died and 90 died. Median PFS was 9.9 months (IQR 5.2–18.3) in arm A and 11.3 months (IQR 7.6–16.3) in arm B. Adjusted HR for arm B versus arm A was 1.04 (95% CI 0.69–1.56, p = 0.854). 107 PFS II events were recorded during the second-line treatment. Median PFS II was 5.3 months (IQR 2.8–7.2) in arm A and 6.1 months (IQR 3.3–8.4) in arm B. Adjusted HR for arm B versus arm A was 0.97 (95% CI 0.65–1.45, p = 0.881). 67 PFS III events were recorded during the third-line treatment. Median PFS III was 4.0 months (IQR 2.5–6.9) in arm A and 4.7 months (IQR 2.8–6.5) in arm B. Adjusted HR for arm B versus arm A was 1.00 (95% CI 0.58–1.70, p = 0.986). Median OS was 12.3 months (IQR 5.7–25.3) in arm A and 18.6 months (IQR 10.7–27.6) in arm B. Adjusted HR for arm B versus arm A was 0.84 (95% CI 0.55–1.28, p = 0.4114.

During the second-line treatment, a complete or partial response was observed in 15 (29%) patients in arm A and in 22 (40%) patients in arm B (p = 0.228). During the third-line treatment, a partial response was observed in 7 (23%) patients in arm A and in 8 (21%) patients in arm B (p = 0.780). Overall, RR was 38% (19 patients) in arm A and 50% (27 patients) in arm B (p = 0.221). A significant interaction between arms and the primary tumour location was detected both for PFS

![Fig. 1. Trial profile.](image-url)
Table 1  
Baseline characteristics of patients included in mITT population.  

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm A (n = 53)</th>
<th>Arm B (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27 (51%)</td>
<td>36 (65%)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (49%)</td>
<td>19 (35%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>61 (56–65)</td>
<td>64 (56–71)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>42 (79%)</td>
<td>43 (80%)</td>
</tr>
<tr>
<td>1</td>
<td>11 (21%)</td>
<td>11 (20%)</td>
</tr>
<tr>
<td><strong>Primary tumour site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>50 (94%)</td>
<td>52 (96%)</td>
</tr>
<tr>
<td>Multiple</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td><strong>Single site specification</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascendient colon</td>
<td>11 (22%)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Hepatic flexure</td>
<td>1 (2%)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>1 (2%)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Splenic flexure</td>
<td>0 (0%)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Descending colon</td>
<td>5 (10%)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>14 (28%)</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Recto-sigmoid junction</td>
<td>18 (36%)</td>
<td>18 (35)</td>
</tr>
<tr>
<td><strong>Metastatic site</strong></td>
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<td></td>
</tr>
<tr>
<td>Lung</td>
<td>10 (19%)</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Liver</td>
<td>29 (55%)</td>
<td>29 (54%)</td>
</tr>
<tr>
<td>Liver and lung</td>
<td>5 (9%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (17%)</td>
<td>10 (19%)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
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<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>48 (91%)</td>
<td>46 (85%)</td>
</tr>
<tr>
<td>Mucoid adenocarcinoma</td>
<td>3 (6%)</td>
<td>7 (13%)</td>
</tr>
<tr>
<td>Signet ring cell carcinoma</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade I: well differentiated</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Grade II: medium differentiated</td>
<td>28 (61%)</td>
<td>36 (71%)</td>
</tr>
<tr>
<td>Grade III: poorly differentiated</td>
<td>11 (24%)</td>
<td>13 (25%)</td>
</tr>
<tr>
<td>Grade IV: indifferenctated</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gx: not evaluable</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
</tr>
</tbody>
</table>

Arm A: irinotecan/cetuximab (II line) and FOLFOX-4 (III line).  
Arm B: FOLFOX-4 (II line) and irinotecan/cetuximab (III line).  
Data are median (IQR) or n (%).  
* Data not available for all mITT patients.

(p = 0.011) and for OS (p = 0.005). A right and left primary tumour location was recorded for 31 (28.7%) and 74 (68.5%) patients, respectively. Two patients had a primary tumour in both the colon locations and the primary site of one patient was unknown. (See Fig. 2)

Thirty patients with right colon as primary site showed progressive disease and 27 died. Median PFS was 7.9 months (IQR 3.4–9.9) in arm A and 10.0 months (IQR 6.6–13.1) in arm B. Adjusted HR for arm B versus arm A was 0.24 (95% CI 0.08–0.74, p = 0.012). Median OS was 8.8 months (IQR 3.4–13.5) in arm A and 12.6 months (IQR 7.8–18.6) in arm B. Adjusted HR for arm B versus arm A was 0.16 (95% CI 0.05–0.52, p = 0.002; Fig. 3).

Sixty-eight patients with left colon as primary site showed progressive disease and 62 died. Median PFS was 10.8 months (IQR 5.8–22.8) in arm A and 13.6 months (IQR 7.7–21.8) in arm B. Adjusted HR for arm B versus arm A was 1.23 (95% CI 0.75–2.01, p = 0.412). Median OS was 13.1 months (IQR 8.4–28.5) in arm A and 20.2 months (IQR 10.8–29.3) in arm B. Adjusted HR for arm B versus arm A was 1.05 (95% CI 0.62–1.78, p = 0.859; Fig. 3).

AEs occurring in at least 10% of patients are summarised in Table 2 and in Table 3. Overall, 13 SAEs from 13 patients have been reported: eight occurred in arm A and five in arm B; 9 had no relationship with treatment, 1 had a probable relationship (with FOLFOX-4 during the second-line treatment) and 3 had a definitive relationship (two with the combination irinotecan/cetuximab during the second-line treatment, one with FOLFOX-4 during the second-line line treatment). No treatment-related SAE had a fatal outcome.

4. Discussion

The global outcome of metastatic colorectal cancer patients has dramatically improved in the last 20 years [16].

The sequential use of chemotherapy and targeted agents, such as those directed against the tumour-driven angiogenesis (bevacizumab, aflibercept, ramucirumab) and those directed against the EGFR (cetuximab, panitumumab), currently represents the cornerstone of the treatment strategy for these patients. Along with the growing development of innovative therapeutic choices the possibility of a more accurate, molecularly-guided, patients selection also introduced the option to further individualise the treatment approach. The routine use of RAS mutational status allowed in fact the exclusion of patients with resistant tumours from a potentially toxic but inactive treatment with anti-EGFR agents. Although different clinical trials and head-to-head comparisons have been conducted the scientific debate on the best first-line option in RAS WT colorectal cancer patients is still unresolved.

In this multifaceted scenario the definition of the optimal therapeutic sequence acquired an increasingly central role in the planning of the global treatment strategy.

However, data on treatment sequence are largely lacking and most of the considerations used in the clinical practice derive almost exclusively from indirect evidences and cross-trials comparisons. The main aim of the COMETS trial was to prospectively explore two different treatment sequences in order to define an optimal therapeutic strategy in K-RAS WT colorectal cancer patients. The trial failed its primary PFS endpoint, nonetheless we observed a trend towards an improved OS in favour of patients included in arm B (HR 0.84, 95% CI: 0.55–1.28; p = 0.41). This observation was not statistically significant possibly as the study was not powered to detect a difference in OS and the sample size was inadequate. This was likely the consequence of the trial amendment limiting study
inclusion to K-RAS WT only patients. The use of K-RAS along with more robust first-line data for anti-EGFR monoclonal antibodies encouraged in fact the use of first-line cetuximab in combination with chemotherapy in these patients (K-RAS WT). Taken together these factors resulted in a lower accrual rate and prompted in turn to a change in the primary end-point from OS to PFS, with the aim to decrease the necessary sample size.

The exclusive use of K-RAS exon 2 mutational status for patients inclusion might represent a further potential bias for data interpretation and analysis. In fact we now know that less frequent K-RAS, N-RAS or BRAF mutations have a definite role in predicting global outcome during anti-EGFR therapy.

The inclusion of K-RAS exon 2 WT only patients and the smaller than initially planned sample size should be both considered as relevant limitations to the interpretation of the results deriving from the present study.

Surprisingly the potential clinical benefit deriving from second-line FOLFOX-4 followed by third-line irinotecan/cetuximab was not apparently associated with a higher activity of cetuximab third-line versus FOLFOX-4 as hypothesised in the trial rationale, but more clearly related to the poor performance of cetuximab second-line.

These findings seemed in accordance with previous observations suggesting that cetuximab was significantly less effective when administered immediately after bevacizumab first-line [17,18]. Notably an analysis from the FIRE-3 trial investigating the impact of subsequent therapies on study outcome suggested that the sequential application of first-line bevacizumab followed by second-line cetuximab resulted in a less favourable efficacy profile than the reverse sequence [19].

Similar suggestions derive from the analysis of two randomised trials such as the PRODIGE-18 (bevacizumab or cetuximab plus chemotherapy after progression on bevacizumab plus chemotherapy) and the SPIRITT (panitumumab or bevacizumab plus FOLFIRI after progression on bevacizumab plus FOLFOX) [20,21].

These data are in accordance with preclinical models suggesting that resistance to cetuximab may arise in presence of an increased expression of vascular endothelial
growth factor (VEGF) with a resultant sensitivity to anti-VEGF agents. On the contrary, a previous treatment with anti-VEGF agents may induce a hypoxic tumour microenvironment, ultimately responsible for the decreased efficacy of EGFR inhibitors as well as the activation of EGFR independent RAS signal [22–27].

In conclusion, the present study was not able to demonstrate any clinically meaningful advantage from
an early (second-line) or delayed (third-line) use of cetuximab in patients progressing after FOLFIRI/Bevacizumab first-line. Interestingly our findings suggest that a previous treatment with bevacizumab may affect cetuximab efficacy. This observation could be particularly relevant in left primary colorectal tumours where first-line EGFR inhibition seems to be a preferable treatment option. These data should be prospectively confirmed before any possible clinical application.

Contributors

Dr. Cascinu contributed for literature search, figures and the final approval. Dr. Cascinu, Dr. Labianca, Dr. Lonardi, Dr. Zaniboni and Dr. Zagonel contributed for the study design. Dr. Cascinu, Dr. Labianca, Dr. Lonardi, Dr. Zaniboni, Dr. Zagonel, Dr. Rosati, Dr. Nasti, Dr. Marchetti, Dr. Leone, Dr. Bilancia, Dr. Iaffaioli, Dr. Giordano, Dr. Corsi, Dr. Ferrau` and Dr. Ronzoni contributed for the data collection, data analysis and data interpretation. Dr. Cascinu, Dr. Labianca, Dr. Lonardi, Dr. Zaniboni, Dr. Zagonel, Dr. Galli and Dr Scartozzi contributed for the manuscript writing. Dr. Galli and Dr. Scartozzi contributed for data analysis and interpretation and review of the manuscript.

Conflict of interest statement

None declared.

Acknowledgements

This study was supported by a grant from AIFA (Agenzia Italiana del Farmaco), grant code: FARM 6XB38F. The authors would like to commemorate their beloved colleague and friend Dr. Irene Floriani from the Mario Negri Institute, who passed away on 12th January 2016 and who dedicated her life to clinical research with infinite passion and skills. Dr. Irene Floriani was involved in the statistical design and coordination of this clinical trial.

References


[11] Venook A, Niedzwiecki D, Lenz HJ, Innocenti F, Mahonei MR, Bert H, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MRC). J Clin Oncol 2014;32(suppl.). LBA3 (abstr).


